REMARKS

I. Introduction

Applicants respectfully request reconsideration of the present application in view of the following reasons and appended evidence.

II. Status of the Claims

This amendment adds, changes and/or deletes claims in this application. A detailed listing of all claims that are, or were, in the application, irrespective of whether the claim(s) remain under examination in the application, is presented, with an appropriate defined status identifier.

Claims 1, 2, 30, 31, 35, and 36 have been amended to recite "wherein the nanoparticulate drug has an effective average particle size of less than about 1000 nm, wherein at least 50% of the drug particles have ~~an average~~ a particle size of less than about 1000 nm . . ." The recitation of "average" twice was improper, as the definition of "an effective average particle size" is the size below which 50% of the drug particles fall.

As the foregoing amendments do not introduce new matter, entry thereof by the Examiner is respectfully requested.

III. The Advisory Action

In the Advisory Action, the PTO responded to Applicants' response dated July 18, 2005, and elaborated upon its reasons for maintaining the three (3) grounds for rejecting the claims over the cited prior art. Applicants now turn to each ground.

A. Rejection of Claims Under 35 U.S.C. § 102(b)

1. Desieno Fails to Teach or Suggest Rate Controlling Polymers

Claims 1, 2, 8-10, 13, 14, 30, 31, and 34-53 stand rejected under 35 U.S.C. § 102(b) as being allegedly anticipated by U.S. Pat. No. 5,573,783 to Desieno et al. ("Desieno"). In maintaining this rejection, the PTO continued to rely upon Desieno for its disclosure of a

polyvinylpyrrolidone (PVP) and polyethylene glycol (PEG) film coating, "namely, the [claimed] rate-controlling polymer." Advisory Action at page 2. Additionally, notwithstanding that Desieno does not describe rate controlling characteristics, the PTO concluded that the presence of the PVP/PEG in the compositions of Desieno inherently imbues controlled release properties to the disclosed compositions. *See id.* at 2-3. Thus, the PTO considers to now have placed the burden of proof upon Applicants to rebut the allegation by showing that Desieno does not inherently teach or suggest controlled release nanoparticulate compositions. Applicants respectfully traverse the rejection.

a. By Contrast to the Claimed Invention, Desieno Teaches Rapid Release Nanoparticulate Compositions

Desieno does not anticipate the claimed invention because the reference explicitly characterizes the PVP/PEG film coat as not impeding the redispersion of drug nanoparticles. Applicants pointed out previously, and the PTO now disputes, that Desieno itself evidences the rapid release characteristics of the disclosed compositions. First, Desieno does not teach or suggest nanoparticulate compositions that comprise at least one rate-controlling polymer.

Second, Desieno flatly states that the disclosed compositions, by contrast to the claimed composition, are not inhibited from redispersing. The reference sets forth a testing procedure to determine the ease of reconstituting particles from the disclosed compositions, *i.e.*, to evaluate the rate of drug particle release. *See* Desieno at col. 17, line 55, to col. 18, line 3. "Reconstituting" particles from the overcoated compositions is no different from "releasing" or "redispersing" particles from the composition. Moreover, the procedure of Desieno is analogous and therefore relevant to Applicants' own testing procedure to evaluate drug particle release rates (*see* specification at page 24, lines 9-19). Thus, Desieno prescribes a shaking time of 10 minutes, which was sufficient for Desieno to conclude that a PVP/PEG overcoat "in particular . . . [does not] inhibit[] redispersion of the drug in aqueous media." *Id.* at col. 18, lines 4-8.

A person who is skilled in the art reading Desieno therefore would harbor absolutely no doubt that the PVP/PEG overcoat taught by Desieno is *not* a rate-controlling polymer. Thus, the composition comprising the overcoat is not a controlled release composition.

b. The Formulation Arts Teach That PVP and PEG Overcoats Result in Rapid Release Compositions

Confirming Desieno's explicit teaching, the formulation arts unequivocally teach that a PVP/PEG film coating, as with Desieno, is to be employed for the manufacture of *rapid release* compositions. "Water-soluble film formers such as . . . polyethylene glycol[] [and] polyvinyl pyrrolidone . . . form a rapidly dissolving barrier. *See* Chang et al. at 238 (submitted with Applicants' response and entered into the record on September 10, 2001). More specific evidence in the art establishes that polyvinylpyrrolidone "dissolves quickly . . . [and] does not delay disintegration or dissolution." *See* Plasdone® Povidone Product Guide, International Specialty Products (2005) (EXHIBIT 1).

By contrast, Chang et al. teach that *controlled release* coatings can be prepared by mixing a water-soluble polymer, such as PVP and PEG, with a hydrophobic polymer to create "dialysis membranes" when the coating is exposed to water. *Id.* at 216-7. The presence of both kinds of polymers is essential to create small pores left by the water-soluble polymer. A person who is skilled in the art, knowing this well-established principle, would apprehend that Desieno does not teach controlled release nanoparticulate compositions because PVP and PEG are both water-soluble polymers and, therefore, they would not be used with each other, as taught by Desieno, to create a controlled release film coating. The inevitable conclusion is that PVP/PEG, when used as a film coating as prescribed by Desieno, is a rapid release coating.

Well-established wisdom in the art thus fortifies the fact that Desieno does not explicitly or inherently teach controlled release nanoparticulate compositions. For these reasons, Desieno does not anticipate the claims. Applicants therefore respectfully urge the PTO to reconsider and withdraw this ground for rejection.

c. Applicants' Use of PVP and PEG as Rate Controlling Polymers

The choice of a rate controlling polymer first depends upon the type of controlled release system to be utilized: *i.e.*, a coating system or a matrix system. See claim 1(b)(i) ("the rate-controlling polymer is integrated in a rate-controlling matrix with the nanoparticulate drug composition or coats the nanoparticulate drug composition"; or the

composition can comprise both a matrix and a coating system). A rate controlling composition utilizing a coating system employs a polymer that forms a water insoluble backbone, such as poly(alkylmethacrylate), as a rate controlling polymer. Water soluble polymers, such as PVP and PEG, can also be used in coating systems, but they must be used in conjunction with a polymer that forms a water insoluble backbone to yield a controlled release composition. *See e.g.,* Declaration under 37 C.F.R. § 1.132 by Rajeev A. Jain, filed with Applicants' response on January 15, 2003. Thus, if the water soluble polymers PVP and PEG are utilized in a coating system in the absence of a polymer that forms a water insoluble backbone, the resulting composition is an immediate release composition, such as that described by Desieno.

Matrix controlled release systems can use as a rate controlling polymer a water soluble polymer having a molecular weight high enough to form a viscous hydrogel. Water soluble polymers such as HPC and HPMC have varying "grades" or molecular weights; high molecular weight polymers are very viscous, and strong, viscous gels resulting from such polymers control the diffusion of water and drug release, producing rate controlling properties. See e.g., pp. 2, 6-7, and 12 of "Formulating for Controlled Release with METHOCEL Premium Cellulose Ethers," The Dow Chemical Company (1995) (EXHIBIT 2).

2. Modi Fails to Teach the Recited Nanoparticulate Drug Composition

Claims 1, 2, 8, 9, 13, 14, 30, 31, 34-38, 41, 42, 45, 46, 49, 50, and 53 stand rejected under 35 U.S.C. § 102(b) as being allegedly anticipated by WO 95/22318 to Modi.[1] As best as Applicants understand the PTO's response to their previous arguments, the PTO appeared to dispute whether Modi teaches a water-soluble drug, stated that Modi teaches the particle size required by the claims, and concluded that Modi anticipates the claimed invention. Advisory Action at page 4. Applicants respectfully traverse for at least three reasons.

[1] Applicants previously referred in error to this reference as "Vernon." The nominal applicant is Modi.

The PTO did not address, and Modi fails to teach or suggest, the claimed requirement that at least one surface stabilizer is associated with the surface of the nanoparticulate drug. There is simply no ignoring this fact.

Additionally, Modi does not address the solubility of the drug. The claims, by contrast, require the drug to be poorly soluble.

Finally, Modi generally describes drug particle sizes falling into the range of 100-100,000 nm (*see* Modi at page 8, lines 23-25). The reference does not teach or suggest, however, that at least 50% of the drug particles have a particle size of less than about 1000 nm when measured by light scattering techniques, as required by the claims.

Because Modi fails to teach or suggest all of these features of the claimed invention, it does not anticipate. Accordingly, Applicants respectfully request the PTO to reconsider and withdraw this ground for rejection.

B. Rejection of Claims Under 35 U.S.C. § 103(a)

Claims 1-22 and 25-53 were rejected previously under 35 U.S.C. § 103(a) as being allegedly unpatentable over Desieno in view of U.S. Pat. No. 5,145,684 to Liversidge et al. ("Liversidge) and U.S. Pat. No. 5,811,388 to Friend et al. ("Friend"). While the Advisory Action does not address the merits of Applicants' previous arguments against this rejection, or even indicate whether this rejection is maintained, the foregoing discussion illuminates in any event why the claims are patentable over the cited combination of references.

The PTO clarified in the Final Office Action, dated February 16, 2005, that Desieno is the primary reference, while Liversidge is cited solely to acknowledge the definition of the particle size distribution recited in, *e.g.*, claim 1. Additionally, the PTO relied upon Friend solely to address the concentration and identity of the rate controlling polymer specified in certain dependent claims.

The claims are patentable over Desieno, Liversidge, and Friend for at least the reason that a person of ordinary skill would not have been motivated to make the cited combination. The ordinary artisan would have clearly understood that the nanoparticulate composition

comprising a PVP/PEG film overcoating taught by Desieno rapidly releases (*e.g.*, 10 minutes) nanoparticulate drug, where PVP/PEG is not a rate controlling polymer combination. *Supra.* Additionally, both Desieno and Liversidge highlight a central feature of nanoparticulate drug formulations as providing immediate and fast release of the drug. *See* Liversidge at col. 1, lines 28-30; Desieno at col. 1, lines 30-33. *See also* Desieno at col. 8, lines 42-44 ("pharmaceutical compositions of this invention give rise to unexpectedly high bioavailability . . . and rapid onset of drug action"). Therefore, the person of ordinary skill, armed with Desieno and Liversidge, would have been motivated, if anything, to make nanoparticulate compositions in the manner prescribed by the references precisely to exploit their rapid release characteristics (*e.g.*, minutes) and the benefits flowing therefrom.

Thus, Desieno, alone or in combination with Liversidge, would not have suggested to the person of ordinary skill a controlled release nanoparticulate drug composition. As applicants pointed out previously, the whole point of making nanoparticulate compositions of poorly soluble drugs is to overcome their inherently slow release and therefore low bioavailability properties. *See e.g.,* Liversidge at col. 1, lines 13-27. Proceeding contrary to accepted wisdom in the art is evidence of nonobviousness. *See In re Hedges*, 783 F.2d 1038, 1041, 228 USPQ 685, 687 (Fed. Cir. 1986). *Cf. United States v. Adams*, 383 U.S. 39, 51-52, 148 USPQ 479, 484 ("known disadvantages in old devices which would naturally discourage the search for new inventions may be taken into account when determining obviousness"); *Arkie Lures, Inc. v. Gene Larew Tackle, Inc.*, 119 F.3d 953, 958, 43 USPQ.2d 1294, 1297 (Fed. Cir. 1997) ("conventional wisdom that a combination should not be made is evidence of unobviousness.").

Desieno and Liversidge could not more starkly frame the conventional wisdom that one should not combine a nanoparticulate drug with a rate controlling polymer so as to obtain a controlled release formulation of nanoparticulate drug. *See Arkie Lures, Inc.*, 119 F.3d at 958, 43 USPQ.2d at 1297. Friend is of no avail because to the extent that it might suggest rate controlling polymers useful for making controlled release compositions, as the PTO surmised, it suggests a drug composition that would frustrate the purpose of the immediate release compositions taught by Desieno and Liversidge.

For all of these reasons, the person of ordinary skill in the art would not have considered the claimed invention to be obvious over Desieno, Liversidge, and Friend. Accordingly, Applicants respectfully urge the PTO reconsider and withdraw this ground for rejection.

IV. Conclusion

The present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested. Examiner Tran is invited to contact the undersigned by telephone if she feels that a telephone interview would advance the prosecution of the present application.

Respectfully submitted,

Date Jan 18, 2006

By Michele M Simkin

FOLEY & LARDNER LLP
Customer Number: 22428
Telephone: (202) 672-5538
Facsimile: (202) 672-5399

Michele M. Simkin
Attorney for Applicant
Registration No. 34,717

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.